The Oncologist®

Letters to the Editor

The Harm in Kratom

We noted the most interesting blog by Don Dizon [1] regarding the potential pulmonary toxicity induced by one (or a combination of several) of the fifteen herbal supplements taken by his patient. To illustrate the real and serious toxicity of such supplements, which are commonly available and unregulated by federal agencies, we present a case of severe hepatic toxicity associated with *kratom*, a plant derivative of increasing use as an alternative psychostimulant. A 23-year-old male presented to the emergency department with 4 days of painless jaundice, light stools, and dark urine, 1 week after last consuming *kratom*, a legally available psychoactive extract from the *Mitragyna speciosa* plant. He began ingesting a powdered form of *kratom* 6 weeks prior, consuming an estimated 85 grams in total. He denied exposure to toxins or medications, other than moderate alcohol and marijuana consumption. Total bilirubin was 7.4 mg/dL, direct bilirubin 5.8 mg/dL, ALKP 225 U/L, ALT 210 U/L, and AST 129 U/L. His INR was 0.9 and albumin 4.6 g/dL. White blood cell count was 5.6 K/uL, with 8% eosinophils. Serologies and viral molecular tests for infectious and autoimmune hepatitis were negative. Liver biopsy was entirely consistent with cholestatic liver injury. His recovery over a 2-week period was uneventful, with a return to normal liver function.

Mitragyna speciosa is a tree indigenous to Southeast Asia. Traditionally, its leaves have been chewed, smoked, or strained into tea for increased energy or medicinal purposes. *Kratom* contains the alkaloids mitragynine and 7-hydroxymitragynine, which, in addition to having broad neurochemical activity, are known opioid agonists, perhaps explaining why *kratom* has been used in the community to mitigate symptoms of opioid withdrawal. Effects are dose-dependent: small doses produce stimulatory effects, and larger doses produce sedation [2].

Reports of *kratom's* adverse effects in Asia focus on dependence and withdrawal. More alarming toxicities have been revealed in the Western literature, perhaps as the result of product adulteration or under-reporting of side effects in Asia. These toxicities include hypertension, nephrotoxicity, seizures, and death from presumed overdose [2]. There have been two prior reports of cholestatic jaundice, in cases occuring within 2 and 8 weeks of onset of drug ingestion [3, 4].

In Thailand, a 2007 survey reported lifetime use prevalence of 2.32%, but similar data are not available from other countries [5]. In the U.S., *kratom* may be purchased on the Internet, in “head shops,” or in convenience stores. Federal data suggest rising use in the U.S., with increasing numbers of reports (one report in 2010, 81 reports in the first 6 months of 2012) from forensic laboratories involving *kratom* detection in human subjects [6].

A better understanding of the potential toxicities of *kratom* will enable physicians to identify this entity as a causative agent of unusual side effects and to warn patients of risks associated with its ingestion.

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Disclosures

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Editor's Note: See the related article, "What's the Harm?" by Don S. Dizon, on pages 1006-1007 of this issue.

For Further Reading:
Esther L. Davis, Byeongsang Oh, Phyllis N. Butow et al. Cancer Patient Disclosure and Patient-Doctor Communication of Complementary and Alternative Medicine Use: A Systematic Review. ***The Oncologist*** 2012;17:1475–1481.

Abstract:

Objective. To explore the nondisclosure of complementary and alternative medicine (CAM) use among cancer patients, including reasons for and outcomes from nondisclosure of CAM use, within the context of patient-doctor communication.

Method. A systematic review was conducted exploring investigations surrounding the communication of CAM use for patients with cancer published until August 2011.

Results. A total of 21 studies were located, which reported a prevalence of CAM use among patients with cancer ranging between 11% and 95%; of these patients, 20% to 77% did not disclose their CAM use. The main reasons for nondisclosure were the doctor's lack of inquiry; patient's anticipation of the doctor's disapproval, disinterest, or inability to help; and patient's perception that disclosure of CAM use is irrelevant to their conventional care. There is some evidence to suggest that patient-doctor communication about the use of CAM was associated with an enhanced patient-doctor relationship and higher patient satisfaction.

Conclusion. Although the use of CAM by patients with cancer is high, patients frequently fail to disclose its use to their health professionals for reasons emanating from both sides of the dyadic patient-doctor relationship. Because a substantial proportion of patients with cancer may use CAM and there is potential for herb- or vitamin-drug interactions, further research in patient-doctor communication about CAM is necessary to maintain patient safety and wellbeing. The development of effective interventions to improve the disclosure of CAM use should be an integral part of this future research.

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Narratives in Oncology

What's the Harm?

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Disclosures of potential conflicts of interest may be found at the end of this article.

One of the questions that I face (and which I am certain many of us do) concerns the use of alternative therapies. Iron chelation therapy, high-dose vitamin C infusions, Chinese herbs—interest in these therapies and others like them are driven by word of mouth ("a friend of a friend"), claims on Web sites, and patients' own curiosity. Cancer is serious, and let's face it—modern medicine has not (yet) found the cure.

What usually follows is a Western medicine-driven explanation—that as physicians, we seek to uphold the Hippocratic Oath: to "first, do no harm" and to understand the diseases we treat and the medications we use. More than that, we seek evidence—of benefit and potential harms of proposed therapies. Indeed, evidence-based medicine has become the mantra that guides many of our decisions. Certainly, there is no uniformity in evidence. I am the first to admit that not all treatments I use are backed by evidence from a randomized clinical trial, the gold-standard that applies to much of medicine, and certainly, to oncology. So physicians rely on the perceived best evidence we can find: systematic reviews, observational studies, clinical guidelines, and expert opinions, and occasionally, anecdotes and case reports.

When it comes to many alternative therapies, the data is too sparse to inform discussions on benefits and/or risks. Once, early in my career, I tried to study Essiac, an herbal remedy that a patient of mine had taken. There was so little data that I had to apply for an Investigational New Drug (IND) application with the U.S. Food and Drug Administration. Sadly, the project was terminated due to lack of interest—I could not find women willing to be randomly assigned to Essiac or to placebo. Hence, my first-hand experience with lack of data when it comes to these treatments.

For most patients, it seems that my explanation is sufficient and they proceed with standard (or evidence-based) therapy. Others make an informed choice and initiate alternative treatment—with my knowledge, so we can watch for drug interactions and toxicities. I am aware, however, there is another group that decides to try alternative treatment but does not want me to know. Perhaps it is because they sense I will be against it or because they do not want to "disappoint" me. But I know some of my patients take treatments without my knowledge—I just never know who "they" are.

The last time I thought about this issue, I was treating a young woman for uterine cancer. She had undergone surgery, chemotherapy, and radiation for a high-grade, early-stage tumor and had done well for about 2 years—until she presented with vaginal bleeding and was found to have metastatic disease. She was devastated that her tumor had returned and was less-than-confident that traditional approaches would help. She started doing research on the Web and discovered alternative options, natural medicines and alternative approaches to treatment available internationally. I encouraged her to consider a clinical trial and offered her one available at our center—it was testing a novel antibody drug conjugate—one that showed promise in other tumors. After much discussion, she chose to pursue the clinical trial.

"Can I take other medications?" she asked.

"Well, it depends. What kind?" I asked.

"I would like to try a vitamin and herbal combination that someone told me about."

"Unfortunately, the protocol does not allow you to take alternative or integrative therapies. We do not know about the safety of other medications, especially with a drug that is still being tested."

"Oh, OK," she said.

I presumed the issue was resolved, so we went about enrollment and then started on the trial. After two cycles, she had experienced a partial response and by cycle 4 she appeared to be veering toward remission. I was elated with these results, and she was too. Following her fourth treatment, however, she called complaining of profound shortness of breath. Looking back, it had been gradual—the effort required to climb a flight of stairs slowly had been increasing, though she never complained of it at the time. Now, she could only take four or five steps before experiencing dyspnea. I was alarmed and brought her in to the clinic where a chest X-ray showed diffuse interstitial infiltrates consistent with pneumonitis.

I looked back at the consent form. This was not listed as a known toxicity, not even among "rare" side effects. I asked her if anything had been different in the past month; had she started taking any medication? Travelled anywhere on her off weeks?

"Well, I did start taking herbal supplements last month," she said.

I looked at her a little dumbfounded. "What kinds of supplements?"

She named off a list of 15 supplements, many of which I had never heard of. As she did, I became angry—not because she had taken these treatments, but because she did so when

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it was expressly forbidden as part of the trial. . .and also because she never told me.

"It's possible that what's happening to your lungs is due to the drug, though it has not been reported that I can see. But it's also possible that any of these supplements could have caused the issue—by itself or through an interaction with the drug we are trying for your cancer," I told her, trying not to sound angry.

She started to cry then. "I never imagined that my supplements could cause a problem. They're natural and I didn't need a prescription or anything for them—and what I saw on the Web made them sound so helpful."

"Well, for now, we need to stop them, and we need to hold off on the trial therapy," I told her. "I want to see you weekly so I can make sure things get better, which I hope will happen."

"OK," she said.

It took time, but she did get better. Unfortunately, the delay from waiting for her lung function to improve was too long, and we were forced to withdraw from the trial due to toxicity. In the end, I could not be sure what had caused her lung function to deteriorate. But, as uncertain I am about that, I am also sad that the possibility of using a drug that seemed to be working was now gone. True, she could have progressed within a few months, but she also could have entered a remission, that all-too-infrequent endpoint that patients—and their physicians—hope for.

Note: This article was previously published in the blog, "Discussions with Don Dizon," January 31, 2017.

DISCLOSURES

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Editor's Note: See the related letter to the editor, "The Harm in Kratom," by Joshua Z. Drago, et al., on pages 1010–1011 of this issue.